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In Vivo Determination of the Complex Elastic Moduli of Cetacean Head Tissue

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LONG-TERM GOALS

The overall goal of this project is to develop and demonstrate a system for non-invasive *in vivo* measurement of the complex elastic moduli (stiffnesses and loss factors) of cetacean head tissues. This system is ultimately intended to provide a portable diagnostic capability for use in stranded animal assessments.

OBJECTIVES

The primary technical objective is to remotely generate and detect mid-frequency elastic waves within the body of a living cetacean and to use the measured propagation parameters of these waves to obtain the complex elastic moduli by inversion. A further technical objective is to extract moduli in this manner for intracranial tissues. This objective carries considerably more technical risk since both the wave-generating ultrasound and the probe ultrasound will be attenuated, distorted and scattered by the passage through the skull. The final objective is to develop a prototype portable version of the technology and use it to perform examinations of stranded animals. Data collected with this system is envisioned to serve two purposes: 1) provide basic knowledge of in-vivo elastic properties, which is non-existent for marine mammals, and 2) provide a potential basis for non-invasive diagnostics of tissue pathologies, both naturally occurring or otherwise induced.

APPROACH

The foundation of the work is the capability to remotely generate elastic waves in soft tissues and observe their propagation with an ultrasound-based non-invasive system. The general approach for generation, reception and interpretation of the tissue wave fields is based on a new medical imaging technology called radiation force elastography[i]. These techniques, which have been demonstrated to some extent on human soft tissues, cannot be directly translated to use on cetacean head tissues due to

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the need to propagate through much thicker tissues and through skull bone, all the while keeping within safety limitations for ultrasound exposure[ii]. The current focus of the *in-vivo* program is to overcome these challenges through novel redesign of the concepts for both elastic wave generation and observation.

An embodiment of the shear wave generation system is being studied wherein a ring-like forcing volume is formed by the ultrasonic source. As the ring radius is changed (through a change in the ultrasonic carrier frequency, for example), a fixed receiver measures the change in phase of the waves converging to the center of the ring. This approach has several potential benefits, the sum of which are expected to directly translate to improvements in the robustness of modulus estimation and safety with respect to ultrasound exposure.

The particle displacements resulting from the remotely generated elastic waves can be detected remotely using a modified version of an ultrasonic Doppler vibration measurement system called NVMS developed at Georgia Tech[iii]. Algorithms are being developed to enable the magnitude and phase of vibration to be determined, as well as the range (tissue depth) along the ultrasonic beam at which the vibration is being measured. By measuring the amplitude and arrival time of the shear wave at two different points (or from waves arriving from two different drive locations, as with the ring force excitation) the propagation speed and loss can be determined.

Elastic waves will be both remotely and directly generated in tissue phantoms and measured both remotely and directly to validate the measurement technique. The elastic properties of tissue phantoms will be obtained from remotely generated and measured data and compared with directly measured and tabulated material values. The noninvasive technique will be repeated for tissue phantoms enclosed in a simulated or hydrated real cetacean skull, and with harvested tissue samples. In-vivo testing will be conducted on Navy dolphins. Ultrasound parameters (peak negative pressure, time averaged intensity) will be consistent with limits established as safe for humans, and ultrasound frequencies will be kept high enough to be far above the highest frequency that is audible to the animals.

WORK COMPLETED

1. Transducer calibration 3-D field calibration scans of the new system transducers were completed. The spatial characteristics were largely as expected from pre-test predictions.

2. Vibrometer development and testing The depth-discriminating ultrasonic vibrometer used for detecting shear waves in soft tissues was further developed with improvements to signal processing algorithms and data collection hardware.

3. Hemorrhage and edema detection study The feasibility study addressing the use of the prototype elastography system to detect hemorrhage or edema was completed.

RESULTS

1. Transducer calibration 3-D field calibration scans of the new system transducers were conducted in fresh water. Unfortunately, both transducers developed leaks and had to be returned to the manufacturer for repair. The shear wave generation transducer was re-scanned after repair and found to be only slightly altered. Both transducers behaved as expected from predictions made during the design phase. The vibrometer transducer, used for shear wave motion detection, showed reduced axial

diffraction lobe strength in the extreme nearfield, apparently due to variations from drive element radial symmetry. The net effect on system performance should be beneficial, reducing nearfield tissue heating. The cumulative lost time for system testing due to transducer leak repairs was over five months – time which will be made up with an aggressive near term schedule.

2. NVMS development An investigation was conducted into the optimal drive signal for the NVMS system. In previous work, this had been considered to be a problem of little interest because the relevant ultrasonic exposure limit is defined by the transmitted signal energy and the signal-to-noise ratio (SNR) is defined by the received signal energy, which is directly proportional to this. It is, however, important to consider the point in the system where the dominant source of noise is introduced to the received signal. This was found to occur after the transduction of the received signal, which permitted the transmitted signal level to be reduced well below currently promulgated exposure limits with no degradation to the SNR. Thus for practical purposes the interrogation signal is limited by its peak rather than its total energy and the SNR of displacement measurements can by improved by reducing the crest factor (CF) of the interrogation signal as is possible in any peak limited system. In order to exploit the potential advantages of this it was necessary to develop techniques for the artifact-free pulse compression of the NIVMS signal and for the cancellation of a direct crosstalk signal that was not directly separable in time from the signal of interest.

Pulse compression is not generally applicable to non-time-invariant systems such as NIVMS, or is applicable in only an approximate sense that relies on assumptions of extremely slow time variance. It is possible to show, however that a pseudo transfer function may be synthesized in the frequency domain that exactly relates the received signals resulting from two different transmitted signals with similar, but not identical, spectra. This is an exact solution to the pulse compression problem that relies on a set of assumptions that are already inherent in the NIVMS post processing: the limited bandwidth and small amplitudes of the motion that is to be measured. The pseudo transfer function is constructed by a flat interpolation of each spectral component relating the measured and the compressed carrier signals (the transfer function of the static component of the system response) across the permissible bandwidth of displacements above and below each carrier tone. This scheme was verified using a numerical model for system performance and, in the absence of noise, it was found to introduce no numerical distortion to the measurements above the level of machine precision for the requisite computations. The scheme was also demonstrated to be effective in an experiment where a point target was set in motion using a high intensity ultrasonic field modulating at a low frequency. It was found that NIVMS detected the same displacement level for short and long (compressed) pulses, but the SNRs of the long pulse measurements were considerably higher, as expected. The significance to the program is that the new pulse compression approach should allow artifact-free measurement of displacements that are 10-20 dB smaller than was observable with short pulses of the same peak amplitude.

An investigation was conducted into component sources of noise in the NIVMS system. The contributions to the noise floor of each of the analog system components were investigated by a comparison of signal-free measurements in a variety of system configurations. The dominant source of non-displacement noise in NIVMS measurements was found to be contributed by the analog-to-digital converter and to be directly related to its dynamic range setting (i.e. bit-noise and distortion). Below this, there was an observable reduction in noise that could be achieved by using a minicircuits ZFL-500 preamplifier as the first receiving stage rather than the LeCroy DA1855A, which was incorporated into the system in 2010. This was appeared to be due to a better impedance match. In an optimal system configuration, it would still be necessary to use the LeCroy DA1855A as a second stage

because it allows for the subtraction of the direct crosstalk signal from the transmitter to the receiver. Below this preamplifier noise, the noise floor appears to be thermal noise of the receiving transducer and can only be reduced relative to the signal by increasing the sensitivity of the receiving transducer, reducing its impedance, or increasing the backscattered pressure either by increasing the sound pressure level in the scattering region of interest and/or by increasing the impedance contrast of that region. In summary, the factors that contribute to NIVMS noise, and thereby impose a limit on minimum detectible displacement, have been studied and are well understood. The current implementation, while not universally optimal, should not impose a limit on the attainable performance of the overall prototype elastography system.

3. Hemorrhage and edema detection study A modeling and experimentation study was completed with the aim of assessing the feasibility of detecting fluid inclusions in viscoelastic solids for application in detecting intracranial hemorrhage or edema. Models of rigidly-encased cylindrical tissue-like volumes with and without fluid inclusions were modeled in 3D using COMSOL Multiphysics (COMSOL, Inc., Burlington, MA 01803). The system was excited using an external, uniaxial (translating) mechanical force. The models showed that the relatively short wavelength in an inclusion containing fluid (emulating coagulating blood) compared to that in the bulk tissue provided contrast to the inclusion region. The effect was enhanced by the fact that wavelengths at practical excitation frequencies (<1kHz) were comparable to expected inclusion dimensions, causing high amplitudes due to resonance. A series of experiments was conducted to attempt to reproduce the finite element model results. Tissue phantoms were made using blue phantom (Blue Phantom, Redmond, WA 98052) as the bulk material, and gelatins of varying concentrations were used to emulate blood at various stages of coagulation. The lab models were excited using a shaker, and the internal motion of the phantom was measured using NIVMS. The test data did not show the presence of fluid inclusions as clearly as the predictions. While the discrepancies are not well understood, future efforts may involve different tissue excitation methods.

IMPACT/APPLICATIONS

There is considerable interest in the development of structural acoustic models for the cetacean head for two main reasons: 1) to better understand biomechanics of sound reception and production in cetaceans, and 2) to understand and hopefully mitigate any harmful effects of man-made sound on their health and behavior. The development and validity of these models is severely limited by an almost complete lack of knowledge of the mechanical properties of the constituent living tissue. There is thus considerable interest in being able to measure these properties *in vivo*. The techniques and instrumentation investigated here should also have biomedical diagnostic application, including non-invasive examinations of stranded animals.

RELATED PROJECTS

Rocking of an acoustically small, asymmetric object in response to an underwater acoustic plane-wave has been predicted by Krysl *et al.*[iv] for hemispheres and Fan *et al.*[v] for hemicylinders. While there seems to be no physical reason why such motion should not exist, physical considerations would seem to indicate that such motion would be quite small. The NIVMS ultrasonic vibrometer developed for the *in vivo* project and a plane wave chamber (also previously developed for ONR) were used to determine the extent to which plane waves can induce rocking in a rigid asymmetric object in water. The setup is shown in Figure 1. Both hemi-cylinders and hemispheres were tested at several frequencies. Rocking motion was clearly observed. The amplitude of the rocking motion relative to

the (well-understood) translational motion was independent of frequency and about the same size (<10%) for both the hemisphere and hemicylinder. In the case of the Schilt paper, the primary motivation for the investigation was the possible relevance to otolith motion and fish hearing. The nature and size of the results make such a connection unlikely.

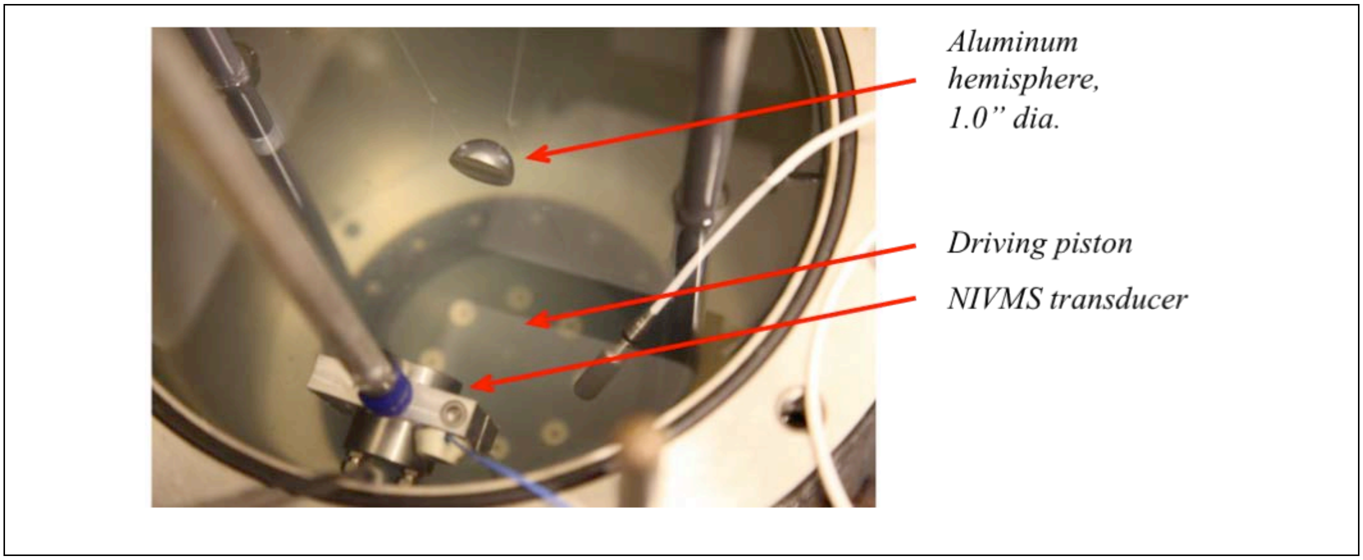

Figure 1. Photograph of experiment setup used to detect rocking of a hemisphere in a plane wave field

PUBLICATIONS

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